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REMARKS

This Amendment is being submitted in response to the Official Action dated 25 January 2008. Claims 1, 4, 7, 8 and 10-25 are herein canceled, claims 26 and 27 are amended, and new claims 28-35 are added. Claims 26-35 remain pending in this application.

Claims 1, 4, 7, 10, 12, 14-16, 17-20 and 24 are rejected under 35 U.S.C. 112, 1st paragraph for non-enablement (the specification does not reasonably provide enablement for the treatment of tumors with the broad genera of agents contemplated by the patent claims). According to the Examiner, there is no direction or guidance for determining the particular agents or administration regimens (e.g., dosages, timing, administration routes, etc.) necessary to treat all of the various tumors. In broad terms the present application teaches a method for treating tumors by increasing the intracellular redox potential, E, above ECCP, and maintaining this higher E for an appropriate duration of time such as to induce selective apoptosis of the cancer cells. The present application teaches that the general method can be implemented by a redox buffer that will raise and maintain the E above the threshold for pRB phosphorylation for up to 75 hours.

The Examiner has rejected the cited claims on the ground that "The specification provides no direction or guidance for determining the particular agents or administration regimens (e.g., dosages, timing, administration routes, etc.) necessary to treat all of the various tumors claimed, particularly in humans." However, the Examiner acknowledges that the disclosure *does* teach and provide direction for four active agents (disulfiram, BCNU, BSO, and curcumin), and shows enablement for these agents as effective in inhibiting cell proliferation in 3T3 fibroblasts, pancreatic and prostate cancer cells, bladder tumor cells, and breast cancer cells. Accordingly, the foregoing amendments to independent claim 26 narrow the claim as suggested

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by the Examiner to specify: 1) the mechanism (decrease in the $[GSH]_2/[GSSG]$ in the malignant cancer cells of said tumor; 2) the enabled agents (any one or a combination from the group of disulfiram, curcumin, BCNU and BSO); and 3) the regimen (continuously maintaining the dephosphorylated state of the RB in said cancer cells continuously within a range of 15 to about 75 hours in order to span at least one cell cycle).

The Examiner cited no scope of enablement problem with claims 26-27, and so especially in light of the present amendments to claims 26-27 which further narrow those claims as suggested by the Examiner, both claims 26-27 as amended should comply with the proper scope of enablement. Claims 27-35 depend from claim 26, add further limitations, and are likewise fully enabled.

Claims 1, 4, 7-8 and 10-25 were rejected under 35 U.S.C. § 102(a) as being anticipated by the inventor's earlier PCT application (WO 02/056823). Instead of completing the PCT requirements for entry into the national stage, this application was filed as a continuation-in-part (CIP) of the PCT application, which in turn claimed priority from the Israeli application filed 01-18-2001. It appears that the PCT priority claim was mistakenly withdrawn in previous prosecution, effectively making the PCT application prior art. Applicant submits herewith a Petition to reinstate the priority claim to the predecessor PCT application and has herein amended the priority claim into the present specification.

In addition, the Examiner suggested either 1) correcting the inventorship in the PCT application or 2) changing the inventorship in the present application. The current inventorship is correct and as stated in Declaration filed previously, the inventorship in the PCT application was incorrect. Accordingly, Applicant has submitted a Request to Change the Inventorship in the PCT application directly to WIPO and a copy of these papers are attached hereto.

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Claims 1, 4, 7-8 and 10-27 were rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,589,987 in view of Huang et al. (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 1/9/2000), Ali-Osman et al. (Mol. Pharm., 1996, vol. 49, pages 1012-1020), Nagendra et al. (Alcohol, 1994, vol. 1, pages 7-10) and Hoffman et al. (J. Theor. Biol., 2001, vol. 211, pages 403-407). According to the Examiner, from the foregoing disclosures it is clear that disulfiram is effective at inhibiting cancer cell proliferation, and that decreasing GSH cell content has a significant effect on the cytotoxicity of the chemotherapeutic drug BCNU. The Examiner contends that the skilled artisan would reasonably expect that administering disulfiram would decrease GSH, increase GSSG (thereby decreasing the $[GSH]^2/[GSSG]$ ratio as recited in the instant claims), and be an effective treatment for tumors.

However, the '987 patent administers disulfiram along with heavy metal ions because heavy metal ions such as copper, zinc, gold, and silver ions significantly enhance the inhibitory effect of disulfiram on tumor cells, while the depletion of such heavy metal ions prevents growth inhibition by disulfiram. This is an entirely different mechanism, and not at all related to raising the intracellular redox potential E above ECCP...the redox potential where cessation of cell proliferation occurs. The Examiner noted that previous claim 26 did not sufficiently reflect the present mechanism and he hinted that more mention of the mechanism in the present claims would be helpful. The amendments to claim 26 clearly reflect the regimen and mechanism of "dephosphorylizing the RB protein in said cancer cells and maintaining a dephosphorylated state of the RB in said cancer cells to induce apoptosis thereof and consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle." None of the cited references teach or suggest the use of disulfiram, curcumin, BCNU or BSO in this capacity toward this end, and so all of

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claims 26-35 are believed to be patentably distinguished.

Applicants note that Hoffman et al. (J. Theor. Biol., 2001, vol. 211, pages 403-407) merely describes the existence of a redox cycle within the cell cycle of normal cells and its absence in cancer cells. This article suggested a selectivity that would result if only the pRB of the cancer cells was dephosphorylated (i.e. the E of the cancer cells was maintained above E_{ccp}), whereas, the phosphorylation state of the pRB of the normal cells was not affected (i.e. the E of the normal cells was not raised above the E_{ccp}). However, this general article lacked the implementation details necessary for enablement as addressed above, and specifically the need to maintain the dephosphorylated state of pRB of the cancer cells for up to 75 hours in order to achieve efficacy.

Claims 1, 4, 7-8 and 10-25 are provisionally rejected on the ground of double patenting over copending Application No. 11/596,043. A proper terminal disclaimer is included herewith to overcome this issue with regard to claims 26-35.

It is believed that all pending claims 26-35 are now allowable, and this application is now in the proper condition. A Notice of Allowance is respectfully requested.

Respectfully submitted,

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